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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/245,198	02/05/1999	JEFFREY BROWNING	A003	4642

7590 07/22/2003

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/22/2003

29

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/245,198	BROWNING ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-4,6-8,10,28,30,31 and 39-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4,6-8,10,28,30,31 and 39-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *05 February 1999* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendments were received and entered as Paper Nos. 25 and 27 on 2/28/03 and 5/16/03, respectively.

Claim 5 and 36-38 were canceled and claims 39-47 were added as requested.

Claims 1-4, 6-8, 10, 28, 30, 31, and 39-47 are pending and under consideration in this Office Action.

After careful reconsideration of the specification and claims, the previous indication of allowability of claims 2 and 4 is withdrawn in view of the following new grounds of rejection.

Claim Rejections - 35 USC § 112

Claims 1-4, 6-8, 10, 28, 30, 31, and 39-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to nucleic acids encoding SEQ ID NOS: 2 or 4, nucleic acids encoding fragments of SEQ ID NO:4 that bind to various cell lines recited in claims 4 and 28, host cells comprising the nucleic acids, and methods of making SEQ I D NO:2, SEQ ID NO:4 or fragments of SEQ ID NO:4. SEQ ID NO:2 is asserted to comprise the amino acid sequence of mouse TRELL. SEQ ID NO:4 is asserted to comprise the amino acid sequence of human TRELL. The specification discloses at

page 16, line 15 that the N-terminal methionine of TRELL is not known. Also no receptor for TRELL has been identified (see page 15, lines 16-19).

The specification asserts that the claimed nucleic acids can be used: 1) to identify new diagnostics and therapeutics for numerous diseases and conditions, 2) to obtain information about and manipulate the immune system and its processes, 3) to directly trigger TRELL-mediated pharmacological events which may have useful therapeutic benefit in the treatment of cancer or the manipulation of the immune system to treat immunologic diseases, 4) for anticancer and immunoregulatory applications to be used in therapies and methods directed to other diseases, 5) to express TRELL under abnormal conditions in a gene therapy setting to enhance anti-tumor immune response or directly affect the survival of a tumor, 6) to affect the survival of an organ graft by altering the local immune response, 7) for use in antisense therapy to inhibit the expression of TRELL, 8) for administering the soluble form of TRELL as a drug to mimic the natural membrane form of TRELL, 10) for use in assays for screening drug candidates which are either agonists or antagonists of the normal cellular function of TRELL or its receptor, 11) to isolate the TRELL receptor (see pages 6-8, 13,16, 24, and 25 of the instant application).

The specification teaches the polynucleotides of SEQ ID NOS 1 and 3, which encode amino acid sequences of SEQ ID NOS: 2 and 4. The specification also teaches the construction of a form of human TRELL lacking the transmembrane region of TRELL, and consisting of some fraction of the extracellular domain of TRELL linked to a secretion signal and a myc epitope tag. See pages 34 and 35. However, it is unclear if

this polypeptide has any TRELL biological activity. The specification discloses a functional test of TRELL activity at page 36, and results are given in Table II on page 37. The test on page 36 discloses only that human TRELL was used in the assay, and does not specify what form of human TRELL was used, soluble or membrane bound. The assay shows that the human TRELL used binds to K562, THP-1, 293, COS, and HT29-14 cells. Further cytotoxicity was induced in HT29-14 cells. However, no cytotoxicity was clearly induced in any other tested cell line including three other carcinoma cell lines.

This rejection is based on the position that the biological function of the claimed nucleic acids is unknown, and one of skill in the art would first have to determine that function before the nucleic acids could be used for any of the purposes set forth in the specification and listed above. The specification indicates at the sentence bridging page 4 and 5, that the biological function of TRELL was not known at the time of filing. Clearly, in order to use TRELL or its nucleic acids to diagnose or treat any disease, one must first establish some correlation between TRELL and the disease. The specification fails to teach any such association. The specification provides very limited guidance regarding methods of gene therapy, generally disclosing that the claimed DNA sequences can be used to express TRELL under abnormal conditions. The sequences could be expressed in tumor cells under the direction of promoters appropriate for such applications and such expression could enhance anti-tumor immune responses or directly affect the survival of the tumor. In addition, the sequences can be used to affect the survival of an organ graft by altering the local immune response (see page 13 of the

specification). However, the specification does not disclose abnormal conditions, other than cancer or organ graft, which can be treated by expressing a polynucleotide encoding TRELL. The specification also fails to disclose the types of tumors in a patient which could be treated by expressing a polynucleotide encoding TRELL, or any alterations in the local immune response as a function of the expression of a polynucleotide encoding TRELL. The specification does not disclose appropriate promoters to use, appropriate target sites for delivery of the polynucleotide, appropriate expression vectors required in the delivery of the polynucleotide, or the level of expression of the polynucleotide such that an anti-tumor response or an alteration in the local immune response is achieved. It is further noted that the specification discloses that only one cell line of eleven cell lines tested *in vitro* displayed any response to a TRELL peptide, and this response required the presence of interferon-gamma (see Table II on page 37 of the instant application). Clearly, the showing in the specification is not sufficient to solve the art-recognized problems associated with gene therapy, as set forth by Verma and Orkin (see Paper Nos. 11 and 15). Because one of skill in the art does not know with what diseases TRELL is or is not associated, and because the in vivo function of TRELL is unknown, these critical pieces of information would have to first be developed before TRELL could be used as a diagnostic, therapeutic, or drug target. Such experimentation is undue because while Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting

material required to practice an invention, **or the conditions under which a process can be carried out**, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the establishment of a relationship with a diseases or a biological processes with which TRELL is associated cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

One might argue that the in vitro test showing that human TRELL caused cytotoxicity in HT29-14 cells is indicative of a use. However, the significance of that test is unknown for at least two reasons. First, the structure of the polypeptide used in the assay is not disclosed, so it is not clear what portion of TRELL, or what 3-dimensional configuration, is required for the function of cytotoxicity. Second, the relevance of HT29-14 cells to disease is unclear. Dermer (BioTechnology (1994) 12: 320) taught that cell lines in which cancer are studied are generally unsuitable for the job because they do not mimic conditions in the human body. Dermer holds that in vitro cell lines are a poor representation of malignancy with characteristics profoundly different from the human disease. This is so because the process of adapting malignant body cells to life

in culture requires the cell to adapt and transform from a cell that is stable and differentiated into one that is not, resulting in a cell that has little if any relevance to the actual disease. So the use of human or mouse TRELL to kill HT29-14 cells is only significant as a means of learning more about the claimed invention, i.e. as a means of learning how TRELL kills HT29-14 cells, and it is highly unpredictable as to whether this has any significance in terms of any of the uses for the nucleic acid asserted in the specification.

Because the in vivo biological function of TRELL was unknown at the time of the invention, because it had not been clearly associated with any disease or disorder, and because the only purpose for using TRELL to kill HT29-14 cells is to learn more about the invention itself, i.e. how TRELL functions to kill HT29-14 cells, one of skill in the art could not use the claimed invention without performing undue experimentation.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for

art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Richard Schnizer, Ph.D.